Package 'ememax'

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Type Package

Title Estimation for Binary Emax Models with Missing Responses and Bias Reduction

Version 0.1.0

Description Provides estimation utilities for binary Emax dose-response models. Includes Expectation-Maximization based maximum likelihood estimation when the binary response is missing, as well as bias-reduced estimators including Jeffreys-penalized likelihood, Firth-score, and Cox-Snell corrections.The methodology is described in Zhang, Pradhan, and Zhao (2025) <doi:10.1177/09622802251403356> and Zhang, Pradhan, and Zhao (2026) <doi:10.1080/10543406.2026.2627387>.

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Depends R (>= 4.0.0), clinDR (>= 2.5.2)

Imports BB, brglm, boot, formula.tools, MASS, maxLik, numDeriv, stats

Suggests knitr, rmarkdown, testthat (>= 3.0.0)

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Contents

`Augment_Missing` *Augment missing response with observed information*

Description

Augment missing response with 0 and 1, and remain all other variables the same.

Usage

```
Augment_Missing(data)
```

Arguments

`data`	Dataset contain missing response indicated as'NA', including response variable as 'y' and dose variable as 'dose'.

Details

DETAILS

Value

A complete dataset with augmentation.

Comp_Hess *Compute analytical form of Hessian matrix of Binary Emax model*

Description

Compute Hessian matrix of Binary Emax model

Usage

```
Comp_Hess(data, theta, weight)
```

Arguments

data	A complete dataset without missingness, including response variable as 'y' and dose variable as 'dose'.
theta	Parameters of Emax model. The order of the variables is (E0,log(ED50),Emax).
weight	A vector of working weight from the EM iterations.

Details

Compute Hessian matrix of Binary Emax model which will be used in finding derivative of Jeffery's prior.

Value

A matrix for Heissian.

Comp_I *Compute analytical form of expected information matrix of Binary Emax model*

Description

Compute expected information matrix of Binary Emax model

Usage

```
Comp_I(data, weight, theta)
```

Arguments

data	A complete dataset without missingness, including response variable as 'y' and dose variable as 'dose'.
weight	A vector of working weight from the EM iterations.
theta	Parameters of Emax model. The order of the variables is (E0,log(ED50),Emax).

Details

Compute expected information matrix of Binary Emax model which will be used in finding derivative of Jeffery's prior.

Value

A matrix of expected information

`comp_Q` *Maximization function estimation of EM algorithm with defined weight.*

Description

Estimate Maximization function with given parameters, weight, and data for the EM Emax model.

Usage

```
comp_Q(data, theta, alpha, weight, mis_form)
```

Arguments

`data`	A complete dataset without missingness, including response variable as 'y' and dose variable as 'dose'.
`theta`	Parameters of Emax model. The order of the variables is (E0,log(ED50),Emax).
`alpha`	Parameters of logisitic missing indicator model.
`weight`	A vector of working weight from the EM iterations.
`mis_form`	an object of class "formula": a symbolic description of the model to be fitted.

Details

Calculating the maximization function of EM algorithm for each iteration.

Value

A value of function estimation

`comp_Q_firth` *Maximization function estimation of bias reduced EM algorithm with defined weight.*

Description

Estimate Maximization function with given parameters, weight, and data for the bias reduced EM Emax model.

Usage

```
comp_Q_firth(data, theta, alpha, weight, fit_mis)
```

Arguments

`data`	A complete dataset without missingness, including response variable as 'y' and dose variable as 'dose'.
`theta`	Parameters of Emax model. The order of the variables is (E0,log(ED50),Emax).
`alpha`	Parameters of logisitic missing indicator model.
`weight`	A vector of working weight from the EM iterations.
`fit_mis`	an object of class "formula": a symbolic description of the model to be fitted.

Details

Calculating the maximization function of bias reduced EM algorithm for each iteration.

Value

A value of function estimation

`comp_theta` *Estimation of emax parameters in EM algorithm iteration.*

Description

Calls Newton-Raphson optimizer MaxNR, for Emax model.

Usage

```
comp_theta(data, weight, theta)
```

Arguments

`data`	A complete dataset without missingness, including response variable as 'y' and dose variable as 'dose'.
`weight`	A vector of working weight from the EM iterations.
`theta`	Initial value of parameters for optimization. The order of the variables is (E0,log(ED50),Emax).

Details

Fits the Emax model with defined working weights using MaxNR.

Value

A vector of parameters of Emax model. The order of the variables is (E0,log(ED50),Emax).

`comp_theta_cox_snell` *Cox–Snell bias-corrected estimator (one-step using* **clinDR** *MLE)*

Description

Starts from the MLE from **clinDR** `fitEmax` and applies a user-supplied Cox–Snell bias correction.

Usage

```
comp_theta_cox_snell(data = NULL, weight = NULL, theta = NULL)
```

Arguments

`data`	A data.frame (or list) with `y` (0/1) and `dose`.
`weight`	Numeric vector of case weights.
`theta`	Numeric(3) initial guess; ignored if **clinDR** MLE succeeds.

Details

Requires helpers `comp_bias()` and `Comp_I_score()` in your package.

Value

A list with:

par bias-corrected parameter vector `c(e0, emax, led50)`.

vc Variance-covariance matrix (generalized inverse of information).

See Also

`fitEmax`

Examples

```
theta_true=matrix(c(qlogis(0.1),qlogis(0.8)-qlogis(0.1),log(7.5)),1,3)
colnames(theta_true)<- c('e_0','emax','led_50')
theta_true <- as.data.frame(theta_true)
dose_set <- c(0,7.5,22.5,75,225)
n=355
data <-sim_data(theta_true,n,dose_set)
res <- comp_theta_cox_snell(data=data )
```

`comp_theta_firth` *Estimation of emax parameters in Jeffery's prior penalized IL algorithm iteration.*

Description

Calls Newton-Raphson optimizer MaxNR, for Emax model.

Usage

```
comp_theta_firth(data, weight, theta)
```

Arguments

`data`	A complete dataset without missingness, including response variable as 'y' and dose variable as 'dose'.
`weight`	A vector of working weight from the EM iterations.
`theta`	Initial value of parameters for optimization. The order of the variables is (E0,log(ED50),Emax).

Details

Fits the Emax model with defined working weights using MaxNR with bias reduction.

Value

A vector of parameters of Emax model. The order of the variables is (E0,log(ED50),Emax).

`comp_theta_firth_score` *Firth-corrected estimating equation solution (score-based)*

Description

Solves the Firth-corrected score equations for an Emax-type binary-response model. Requires user-provided score and information helpers.

Usage

```
comp_theta_firth_score(data = NULL, weight = NULL, theta = NULL)
```

Arguments

`data`	A data.frame (or list) with at least `y` (0/1) and `dose`.
`weight`	Numeric vector of case weights, same length as `data$y`.
`theta`	Numeric vector (length 3): `c(e0, emax, led50)` for initialization.

Details

This function depends on internal helpers you must supply in the package: `Score_e0()`, `Score_emax()`, `Score_led50()`, `Comp_Fish_inf()`, and `Comp_I_score()`.

Value

A list with elements:

par numeric(3) estimated parameters.

Fisher.inf Observed/expected information matrix at the solution (from `Comp_I_score`).

vc Fisher-based variance/covariance (from `Comp_Fish_inf`).

score Score vector evaluated at the solution.

See Also

`fitEmax`

Examples

```
theta_true=matrix(c(qlogis(0.1),qlogis(0.8)-qlogis(0.1),log(7.5)),1,3)
colnames(theta_true)<- c('e_0','emax','led_50')
theta_true <- as.data.frame(theta_true)
dose_set <- c(0,7.5,22.5,75,225)
n=355
data <-sim_data(theta_true,n,dose_set)
res <- comp_theta_firth_score(data=data )
```

comp_theta_jeffrey *Jeffreys-penalized likelihood estimator via Newton–Raphson*

Description

Maximizes the Jeffrey's prior-penalized log-likelihood for the binary Emax model using `maxLik::maxNR`.

Usage

```
comp_theta_jeffrey(data = NULL, weight = NULL, theta = NULL)
```

Arguments

`data`	A data.frame (or list) with `y` (0/1) and `dose`.
`weight`	Numeric vector of case weights.
`theta`	Numeric(3) initial guess `c(e0, emax, led50)`.

Details

Requires helpers `Comp_Hess()`, `Comp_I()`, and `Comp_Hess_deriv()` that compute the (penalized) Hessian, information, and derivatives of the Hessian.

Value

A list with:

par Estimated parameter vector.

hessian Final Hessian returned by optimizer.

vc Fisher-based variance/covariance.

See Also

`fitEmax`

Examples

```
theta_true=matrix(c(qlogis(0.1),qlogis(0.8)-qlogis(0.1),log(7.5)),1,3)
colnames(theta_true)<- c('e_0','emax','led_50')
theta_true <- as.data.frame(theta_true)
dose_set <- c(0,7.5,22.5,75,225)
n=355
data <-sim_data(theta_true,n,dose_set)
res <- comp_theta_jeffrey(data=data )
```

comp_vcov — *Calculate the variance covariance matrix of estimated parameters by EmaxEM*

Description

This provides the estimated VCOV matrix of parameters using IL method by EmaxEM.

Usage

```
comp_vcov(em.emax.fit)
```

Arguments

em.emax.fit	an object for result from EmaxEM

Details

Internal function for variance covariance estimation.

Value

A list of two variance covariance matrices, one for Emax model parameter, one for logistic missing model parameter.

See Also

ginv inv.logit

comp_vcov_firth — *Calculate the variance covariance matrix of estimated parameters by EmaxEM_firth*

Description

This provides the estimated VCOV matrix of parameters using FIL method by EmaxEM_firth.

Usage

```
comp_vcov_firth(em.emax.fit)
```

Arguments

em.emax.fit	an object for result from EmaxEM_firth

Details

Internal function for variance covariance estimation.

Value

A list of two variance covariance matrices, one for Emax model parameter, one for logistic missing model parameter.

See Also

ginv inv.logit

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comp_weight *Estimation of working weight in EM algorithm iteration.*

Description

Internal function for estimating the observation weights for each iteration of EM algorithm.

Usage

```
comp_weight(data, theta, alpha, mis_form)
```

Arguments

data	A complete dataset without missingness, including response variable as 'y' and dose variable as 'dose'.
theta	Parameters of Emax model. The order of the variables is (E0,log(ED50),Emax).
alpha	Parameters of logisitic missing indicator model.
mis_form	an object of class "formula": a symbolic description of the model to be fitted.

Details

Calculating the working weights of EM algorithm for each iteration.

Value

A vector of weights for each observation in the data.

`fitEmaxEM` *Fitting IL method with Emax model and binary response missing data.*

Description

This provides the estimates using IL method.

Usage

```
fitEmaxEM(
  data = NULL,
  theta_0 = NULL,
  alpha_0 = NULL,
  mis_form = as.formula(mis ~ y + dose + x1 + x2)
)
```

Arguments

`data`	Dataset contain missing response indicated as'NA', including response variable as 'y' and dose variable as 'dose'.
`theta_0`	Initial value of Emax model parameters for optimization, Default: NULL
`alpha_0`	Initial value of logistic missingness model parameters for optimization., Default: NULL
`mis_form`	an object of class "formula": a symbolic description of the model to be fitted, Default: as.formula(mis ~ y + dose + x1 + x2)

Value

list of fitted values:

`theta`	the final fitted parameters of Emax model
`alpha`	the final fitted parameters of logistic missing model
`weight`	the final fitted weight for each observation in EM
`Q`	the value of Q function for maximizationfor each iteration of EM
`K`	the total number of iterations of EM to converge
`vcov_theta`	the estimated variance covariance matrix of theta
`vcov_alpha`	the estimated variance covariance matrix of alpha

See Also

`fitEmax`

Examples

```
theta_true=matrix(c(qlogis(0.1),qlogis(0.8)-qlogis(0.1),log(7.5)),1,3)
colnames(theta_true)<- c('e_0','emax','led_50')
theta_true <- as.data.frame(theta_true)
dose_set <- c(0,7.5,22.5,75,225)
n=355
alpha_true = c(0.5,1,-0.5,0,0) #mis 15 typical
data <-sim_data(theta_true,n,dose_set,alpha_true)
res <- fitEmaxEM(data=data$data,mis_form=as.formula(mis~y+dose) )
```

`fitEmaxEM_firth` *Fitting bias reduced IL method with Emax model and binary response missing data.*

Description

This provides the estimates using FIL method.

Usage

```
fitEmaxEM_firth(
  data = NULL,
  theta_0 = NULL,
  alpha_0 = NULL,
  mis_form = as.formula(mis ~ y + dose + x1 + x2)
)
```

Arguments

`data`	Dataset contain missing response indicated as'NA', including response variable as 'y' and dose variable as 'dose'.
`theta_0`	Initial value of Emax model parameters for optimization, Default: NULL
`alpha_0`	Initial value of logistic missingness model parameters for optimization., Default: NULL
`mis_form`	an object of class "formula": a symbolic description of the model to be fitted, Default: as.formula(mis ~ y + dose + x1 + x2)

Value

list of fitted values:

`theta`	the final fitted parameters of Emax model
`alpha`	the final fitted parameters of logistic missing model
`weight`	the final fitted weight for each observation in EM
`Q`	the value of Q function for maximizationfor each iteration of EM
`K`	the total number of iterations of EM to converge
`vcov_theta`	the estimated variance covariance matrix of theta
`vcov_alpha`	the estimated variance covariance matrix of alpha

See Also

fitEmax

Examples

```
theta_true=matrix(c(qlogis(0.1),qlogis(0.8)-qlogis(0.1),log(7.5)),1,3)
colnames(theta_true)<- c('e_0','emax','led_50')
theta_true <- as.data.frame(theta_true)
dose_set <- c(0,7.5,22.5,75,225)
n=355
alpha_true = c(0.5,1,-0.5,0,0) #mis 15 typical
data <-sim_data(theta_true,n,dose_set,alpha_true)
res <- fitEmaxEM_firth(data=data$data,mis_form=as.formula(mis~y+dose) )
```

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log_Emax_i *Log likelihood estimation of binary Emax model*

Description

Estimate Log likelihood of given parameters with data for binary Emax model.

Usage

```
log_Emax_i(data, theta)
```

Arguments

data	A complete dataset without missingness, including response variable as 'y' and dose variable as 'dose'.
theta	Parameters of Emax model. The order of the variables is (E0,log(ED50),Emax).

Details

Internal function of calculating the maximization function of EM algorithm.

Value

A vector of log likelihood of each observation.

log_missing_i *Log likelihood estimation of logisitic missing indicator model*

Description

Estimate Log likelihood of given parameters with data for logisitic missing indicator model.

Usage

```
log_missing_i(data, alpha, mis_form)
```

Arguments

data	A complete dataset without missingness, including response variable as 'y' and dose variable as 'dose'.
alpha	Parameters of logisitic missing indicator model.
mis_form	an object of class "formula": a symbolic description of the model to be fitted.

Details

Internal function of calculating the maximization function of EM algorithm.

Value

A vector of log likelihood of each observation.

sim_data *Simulate dataset for testing Emaxem and Emaxem_firth*

Description

FUNCTION_DESCRIPTION

Usage

```
sim_data(theta, n, dose_set, alpha = NULL)
```

Arguments

theta	True parameters of Emax model. The order of the variables is (E0,log(ED50),Emax).
n	number of observations.
dose_set	A vector indicate the dose set for the dose-response relationship.
alpha	True parameters of logisitic missing model.

Details

DETAILS

Value

A list of two datasets. One is with missingness on repsonse, and the other is the full complete data.

Examples

```
 #EXAMPLE1
 theta_true=matrix(c(qlogis(0.1),qlogis(0.8)-qlogis(0.1),log(7.5)),1,3)
colnames(theta_true)<- c('e_0','emax','led_50')
theta_true <- as.data.frame(theta_true)
dose_set <- c(0,7.5,22.5,75,225)
n=355
alpha_true = c(0.5,1,-0.5,0,0) #mis 15 typical
data <-sim_data(theta_true,n,dose_set,alpha_true)
```

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